Examining the impact of research misconduct, and delays to its correction, on vitamin K reviews and guidelines

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*University of Auckland, New Zealand
None of the authors has a conflict of interest to disclose.

All authors wish to improve the integrity of the research literature in order to minimise the impact of research misconduct on patient care.
2006 - during work on a Cochrane review

Amelioration of osteopenia and hypovitaminosis D by 1α-hydroxyvitamin D3 in elderly patients with Parkinson’s disease

Yoshihiro Sato, Seiji Manabe, Haruko Kuno, Kotaro Oizumi

2007 – First contacted JAMA Internal Medicine

Identical data for falls in three different RCTs with different trial populations. Striking reductions in hip fracture.

Amelioration of osteoporosis and hypovitaminosis D by sunlight exposure in stroke patients

Yoshihiro Sato, MD; Norifumi Metoki, MD; Jun Iwamoto, MD; and Kei Sato, MD

Amelioration of Osteoporosis by Menatetrenone in Elderly Female Parkinson’s Disease Patients With Vitamin D Deficiency

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Abstract—Background: The authors’ previous investigations have disclosed low serum 25-hydroxyvitamin D (25-OH D) concentrations in 45 patients during long-term hospitalization following stroke (mean 5.9 ng/mL). This 25-OH D deficiency resulted from sunlight deprivation. Objective: To evaluate the efficacy of sunlight exposure in increasing serum 25-OH D, in reducing the severity of osteoporosis in bone mineral density (BMD), and in decreasing the risk of hip fractures in chronically hospitalized, disabled stroke patients. Methods: In a 12-month randomized and prospective study of stroke patients, 120 received regular sunlight exposure for 12 months, and the remaining 120 (sunlight-deprived) did not. Results: At baseline, patients of both groups showed vitamin D deficiency: BMD increased by 3.1% in the sunlight-exposed group and decreased by 3.3% in the sunlight-deprived group (p = 0.0601). 25-OH D level increased by fourfold in the sunlight-exposed group. Six patients sustained hip fractures on the hemiplegic side in the sunlight-deprived group, and one hip fracture occurred among the sunlight-exposed group (p = 0.242; odds ratio = 6.1). Conclusion: Sunlight exposure can increase the BMD of vitamin D-deficient bone by increasing 25-OH D concentration.

There was no significant difference between the two groups in the number of falls per subject during the 12 months (1.3 ± 1.9 in the untreated group and 1.4 ± 1.8 in the vitamin K group).
Vitamin K and the Prevention of Fractures
Systematic Review and Meta-analysis of Randomized Controlled Trials
Sarah Cockayne, MSc; Joy Adamson, PhD; Susan Lanham-New, PhD; Martin J. Shearer, PhD, MRCPath; Simon Gilbody, DPhil; David J. Torgerson, PhD

<table>
<thead>
<tr>
<th>Study</th>
<th>Favors Vitamin K</th>
<th>Favors Control</th>
<th>OR (95% CI)</th>
<th>% Weight</th>
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<td>0.23 (0.12 to 0.47)</td>
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<td>0.40 (0.25 to 0.65)</td>
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<td>All Nonvertebral</td>
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<td>0.19 (0.11 to 0.35)</td>
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</table>

Peto odds ratio for hip fractures: 0.23 (95% CI 0.12-0.47)

Peto odds ratio for vertebral fractures: 0.40 (95% CI 0.25-0.65)

Peto odds ratio for all nonvertebral fractures: 0.19 (95% CI 0.11-0.35)
Vitamin K and the Prevention of Fractures

Systematic Review and Meta-analysis of Randomized Controlled Trials

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Peto odds ratio for vertebral fractures: 0.40 (95% CI 0.25-0.65)

Peto odds ratio for all nonvertebral fractures: 0.19 (95% CI 0.11-0.35)
‘Because 1 of the centers provided most of the data for hip fractures..... Sensitivity analysis excluding data from this center.

‘The OR for hip fractures for the remaining 2 studies when combined was 0.30 (still a large effect); however, this finding was no longer statistically significant (95% CI, 0.05-1.74, P=0.18).’

Sato et al. Bone 2002; 31: 114-8

Trials with hip fracture data:
RR 0.20 (95% CI 0.13 to 0.30)
P < 0.00001
Menatetrenone slightly increased bone mineral density (BMD) and reduced vertebral and non-vertebral fractures
Refer to Cockayne systematic review, but do not reproduce figure.

(Also refer to 2 other Sato/Iwamoto RCT reports.)
Still refer to Cockayne review.

Also refer to one review by Iwamoto and Sato and 3 other RCT reports.
In 2013 we undertook a detailed investigation of Sato’s published RCT reports, paper submitted to JAMA

- 33 RCTs published over 15y
  - Statistical evidence that randomisation was extremely unlikely to have occurred
  - Implausible productivity
  - Implausible recruitment rates
  - Implausibly positive outcome data
  - Concerns about ethical oversight
  - Self-plagiarism
  - Absence of funding statements
  - Trials submitted for publication before closing date, duplicated data...
• For RCTs 513 baseline variables
  • 52% of p-values were >0.8
  • 6%, 14%, and 27% of p-values were <0.2, <0.4, and <0.6, respectively.
  • Highly unlikely to have arisen by chance (P=5.2*10^{-82}).
JAMA network publications in 2005

**ORIGINAL INVESTIGATION**

Risedronate Sodium Therapy for Prevention of Hip Fracture in Men 65 Years or Older After Stroke

Yoshihiro Sato, MD; Jun Iwamoto, MD; Tomohiro Kanoko, PhD; Kei Satoh, MD

Background: There is a high incidence of hip fractures in patients after hemiplegic stroke. Bone mineral density decreased on the hemiplegic side in patients after stroke, correlating with the immobilization-induced bone resorption, the degree of paralysis, and hypovitaminosis D. The purpose of this study is to evaluate the effect of risedronate sodium on bone mineral density, bone turnover, and the risk of hip fractures in men 65 years or older after stroke.

Methods: We conducted an 18-month randomized, double-blind, placebo-controlled trial comparing risedronate sodium (5 mg once weekly) and placebo in men 65 years or older after stroke. The primary outcomes were bone mineral density and the risk of hip fractures in patients with a previous stroke.

Effect of Folate and Mecobalamin on Hip Fractures in Patients With Stroke

Yoshihiro Sato, MD
Yoshiaki Honda, MD
Jun Iwamoto, MD
Tomohiro Kanoko, PhD
Kei Satoh, MD

**PRELIMINARY COMMUNICATION**

A Randomized Controlled Trial

The Prevention of Hip Fracture With Risedronate and Ergocalciferol Plus Calcium Supplementation in Elderly Women With Alzheimer Disease

Yoshihiro Sato, MD; Tomohiro Kanoko, PhD; Kei Satoh, MD; Jun Iwamoto, MD

Background: A high incidence of fractures, particularly of the hip, represents an important problem in patients with Alzheimer disease (AD), who are prone to falls and have osteoporosis. We previously found that deficiency of 25-hydroxyvitamin D and compensatory hyperparathyroidism cause decreased bone mineral density in female patients with AD. We address the possibility that treatment with risedronate sodium prevents hip fractures in patients with Alzheimer disease.

**Context** Stroke increases the risk of subsequent hip fracture by 2 to 4 times. Hyperhomocysteinemia is a risk factor for both ischemic stroke and osteoporotic fractures in elderly men and women. Treatment with folate and mecobalamin (vitamin B<sub>12</sub>) may improve hyperhomocysteinemia.

**Objective** To investigate whether treatment with folate and vitamin B<sub>12</sub> reduces the incidence of hip fractures in patients with hemiplegia following stroke.
What happened

- Our detailed statistical analyses paper submitted to JAMA March 2013
- JAMA Expression of Concern May 2015, but our paper was not published. Appears no other journals informed.
- We contacted 4 other journals in 2015, 1 immediately publishes EOC, 3 decline our paper.
- Author “confesses” to the journal Neurology early 2016
- Retractions start in mid 2016
- Neurology notifies all other journals Sept 2016
Systematic review and statistical analysis of the integrity of 33 randomized controlled trials

Mark J. Bolland, MBChB, PhD
Alison Avenell, MBBS, MD
Greg D. Gamble, MSc
Andrew Grey, MD

ABSTRACT

Background: Statistical techniques can investigate data integrity in randomized controlled trials (RCTs). We systematically reviewed and analyzed all human RCTs undertaken by a group of researchers, about which concerns have been raised.

Methods: We compared observed distributions of p values for between-groups differences in baseline variables, for standardized sample means for continuous baseline variables, and for differences in treatment group participant numbers with the expected distributions. We assessed productivity, recruitment rates, outcome data, textual consistency, and ethical oversight.

Results: The researchers were remarkably productive, publishing 33 RCTs over 15 years involving large numbers of older patients with substantial comorbidity, recruited over very short periods. Treatment groups were improbably similar. The distribution of p values for differences in baseline characteristics differed markedly from the expected uniform distribution (p = 5.2 × 10⁻³⁵). The distribution of standardized sample means for baseline continuous variables and the differences between participant numbers in randomized groups also differed markedly from the expected distributions (p = 4.3 × 10⁻⁴, p = 1.5 × 10⁻⁵, respectively). Outcomes were remarkably positive, with very low mortality and study withdrawals despite substantial comorbidity. There were very large reductions in hip fracture incidence, regardless of intervention (relative risk 0.22, 95% confidence interval 0.15-0.31, p < 0.0001, range of relative risk 0.10-0.33), that greatly exceed those reported in meta-analyses of other trials. There were multiple examples of inconsistencies between and within trials, errors in reported data, misleading text, duplicated data and text, and uncertainties about ethical oversight.

Conclusions: A systematic approach using statistical techniques to assess randomization outcomes can evaluate data integrity, in this case suggesting these RCT results may be unreliable.

Neurology® 2016;87:1-12
3 vitamin K Sato trial reports in Cockayne review cited

- Retracted September 2018 (24 months to retract)
- Cited 75 times, incl Dec 2018

Sato et al. Bone 2002; 31: 114-8
- Retracted December 2017 (15 months to retract)
- Cited 54 times, incl Dec 2015

- Retracted December 2017 (15 months to retract)
- Cited 42 times, incl Jan 2018
‘2 of the trials have been retracted...

..we undertook a sensitivity analysis excluding data...

The OR for hip fractures for the remaining 2 studies when combined was 0.30 (still a large effect); however, this finding was no longer statistically significant (95% CI, 0.05-1.74; P=0.18).

Remaining data now rely on only 3 participants with hip fracture from 440 participants in 2 trials
Randomized controlled study on the prevention of osteoporotic fractures (OF study): a phase IV clinical study of 15-mg menatetrenone capsules

Tetsuo Inoue · Toshiharu Fujita · Hideaki Kishimoto · Toshitaka Makino · Tetsuro Nakamura · Toshitaka Nakamura · Tosiya Sato · Kaoru Yamazaki

‘In conclusion, menatetrenone therapy was not effective for preventing vertebral fractures in the full analysis set of this study, but the results suggested that it may prevent vertebral fractures in patients with more advanced osteoporosis.’ Post hoc subgroup analysis.

"The rates of any incident fracture were similar between the two groups (incidence rate ratio 1.074, 95 % confidence interval 0.811-1.422, \( p = 0.62 \)), implying that the primary end point was not met."
Reviews from Japanese group

- 10 reviews of vitamin K 2003-2014
- One retracted to date
- Cited own publications median 4.5 times (range 1 to 11)
- These reviews have been cited 255 times
  - Curr Pharmaceutical Design 2004;10:2557-76
  - Last cited Mar 2019 (49 citations)
  - Nutr Res 2009;29:221-8
  - Last cited Feb 2019 (60 citations)
  - Nutrients 2014;6:1971-80
  - Last cited Mar 2019 (33 citations)
Conclusions 12 years later….

- Concerns were first raised in 2007, but no investigation was initiated until 2013, retractions from only 2016.
- 6/33 RCT reports are still unretracted.
- 45 other publications from this group have been retracted.
- Vitamin K trial reports in a systematic review influenced 2011 Japanese guidance, and possibly led to subsequent trials.
- We have only examined the influence of 3 RCT reports here. Other reports have been quoted by systematic reviews and guidelines in relation to vitamin D and bisphosphonates, fractures and falls prevention, particularly for people with stroke, dementia and Parkinson’s disease.
Conclusions 12 years later….

- Although journals, publishers and institutions have slowly undertaken limited investigations, there has been
  - No official coordination to investigate misconduct
  - No official coordination to ensure the integrity of the scientific literature
- No system exists to alert authors that references they cite have subsequently been retracted
- Ineffective systems for dealing with research misconduct risk inappropriate or ineffective treatments for patients.
Acknowledgements

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Mari Imamura, Research Fellow and native Japanese speaker (University of Aberdeen, UK).

Bill Gillespie (Hull York Medical School, UK).

Lesley Gillespie (University of Otago, New Zealand).

Numerous colleagues who listened and advised.
‘There was truth and there was untruth, and if you clung to the truth even against the whole world, you were not mad.’

George Orwell

*Nineteen Eighty-Four*
Review Article

Vitamin K and the Prevention of Fractures: Systematic Review and Meta-analysis of Randomized Controlled Trials

Sarah Cockayne, MSc; Joy Adamson, PhD; Susan Lanham-New, PhD; et al.

Correction
Our letter:
‘the data in the updated analysis do not justify statements in the study abstract that the effect of vitamin K on hip fracture is ‘still a large effect’ when analyses are based on only 3 hip fractures...

Torgerson’s reply:
‘the findings from our review should, at best, be used to inform future research studies that could confirm or refute the suggestion that there might be a clinically important difference in fracture rates using vitamin K supplements rather than informing current clinical practice.’